HYALURONIC ACID-BASED GELS INCLUDING LIDOCAINE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 15/443,080, filed on Feb. 27, 2017, which is a continuation of U.S. patent application Ser. No. 14/754,504, filed on Jun. 29, 2015, which is a continuation of U.S. patent application Ser. No. 14/242,752, filed on Apr. 1, 2014, which is a continuation of U.S. patent application Ser. No. 13/419,079, filed Mar. 13, 2012, now U.S. Pat. No. 8,822,676, which is a continuation of U.S. patent application Ser. No. 12/393,884, filed Feb. 26, 2009, now U.S. Pat. No. 8,357,795, which claims the benefit of each of U.S. Provisional Patent Application No. 61/085,956, filed Aug. 4, 2008, U.S. Provisional Patent Application No. 61/087,934, filed Aug. 11, 2008, and U.S. Provisional Patent Application No. 61/096,278, filed Sep. 11, 2008, the entire disclosure of each of these applications being incorporated herein by this reference.

FIELD OF THE INVENTION

The present invention generally relates to injectable soft tissue fillers and more specifically relates to hyaluronic acid-based dermal and subdermal fillers including an anesthetic agent.

BACKGROUND

It is generally accepted that as a person ages, the face begins to show effects of gravity, sun-exposure, and years of facial muscle movement, such as smiling, frowning, chewing and squinting. The underlying tissues that keep the skin appearing youthful begin to break down, often resulting in laugh lines, smile lines, "crow's feet" and facial creases often referred to as the "effects of aging."

In an effort to treat or correct the effects of aging, soft tissue fillers have been developed to help fill in facial lines and depressions and for restoring fat loss-related tissue volume loss. The soft tissue fillers thereby temporarily restore a smoother, more youthful appearance.

Ideally, soft tissue fillers are long-lasting, soft, smooth and natural appearing when implanted in the skin or beneath the skin. Further, soft tissue fillers are easy to implant into a patient using a fine gauge needle and require low extrusion force for injection. Ideal fillers would also cause no adverse side effects, and would be injectable with minimal or no discomfort to the patient.

Collagen based soft tissue fillers were developed over 20 years ago, and for some time, bovine collagen-based fillers were the only U.S. Food and Drug Administration (FDA)-approved dermal fillers. Because these dermal fillers are bovine based, one of the main disadvantages has been the potential for allergic reaction in patients. It is believed that approximately 3-5% of human subjects show serious allergic reactions to bovine collagen, thus requiring careful testing before using these fillers in any particular person. In addition to allergic reactions, collagen based fillers degrade rapidly upon injection and require frequent treatments to sustain a smoother, more youthful appearance.

In February 2003, human-derived collagen filler compositions received FDA approval. These collagens provide the advantage of a significantly reduced risk of allergic reactions. However, despite the reduced incidence of allergic reactions, the human derived collagen fillers still suffered from the rapid degradation of the injected product.

The search for fillers that do not provoke allergic reactions and sustain a smoother, more youthful appearance has brought about the development of hyaluronic acid (HA)-based products. In December 2003, the first HA-based filler was approved by the FDA. This was rapidly followed by the development of other HA-based fillers.

HA, also known as hyaluronan, is a naturally occurring, water soluble polysaccharide, specifically a glycosaminoglycan, which is a major component of the extra-cellular matrix and is widely distributed in animal tissues. HA has excellent biocompatibility and does not cause allergic reactions when implanted into a patient. In addition, HA has the ability to bind to large amounts of water, making it an excellent volumizer of soft tissues.

The development of HA-based fillers which exhibit ideal in vivo properties as well as ideal surgical usability has proven difficult. For example, HA-based fillers that exhibit desirable stability properties in vivo, can be so highly viscous that injection through fine gauge needles is difficult. Conversely, HA-based fillers that are relatively easily injected through fine gauge needles often have relatively inferior stability properties in vivo.

One method to overcome this problem is to use crosslinked HA-based fillers. Crosslinked HA is formed by reacting free HA with a crosslinking agent under suitable reaction conditions. Methods of preparing HA based soft tissue fillers including both crosslinked and free HA are well known.

It has been proposed to incorporate certain therapeutic agents, for example, anesthetic agents such as lidocaine, into injectable HA-based compositions. Unfortunately, HA-based injectable compositions which incorporate lidocaine during the manufacturing process are prone to partial or almost complete degradation prior to injection, particularly during high temperature sterilization steps and/or when placed in storage for any significant length of time.

It is an objective of the HA-based soft filler compositions and methods of making and using them as described herein to provide soft tissue fillers that do not cause allergic reactions in patients, are biocompatible and are stable and usable in vivo and include one or more local anesthetic agents.

SUMMARY

The present description relates to soft tissue fillers, for example, dermal and subdermal fillers, based on hyaluronic acid (HA) and pharmaceutically acceptable salts of HA, for example, sodium hyaluronate (NaHA). HA-based compositions described herein include a therapeutically effective amount of at least one anesthetic agent. In one embodiment, for example, the anesthetic agent is lidocaine. The present HA-based compositions including at least one anesthetic agent have an enhanced stability, relative to conventional HA-based compositions including, for example, lidocaine, when subjected to sterilization techniques such as autoclaving, and/or when stored for long periods at ambient temperature. Methods for preparing such HA-based compositions are also provided as well as products made by such methods.

Described herein are soft tissue filler compositions, the compositions generally comprising: a hyaluronic acid component crosslinked with a crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidyloxybutane, 1,2-bis(2,3-epoxypropoxy)ethyl ene and 1-(2,3-